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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SMITH, CAROLYN L	
ART UNIT	PAPER NUMBER
1631	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/885,827	SALVATI ET AL.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/9/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *8 and 10-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-24* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,8,10-12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' election with traverse of Group I (claims 1-7 and 9) in Paper No. 14, filed 12/9/02, is acknowledged. Claims 8 and 10-24 are withdrawn from consideration as being drawn to non-elected Groups.

Applicants' traversal is on the grounds that the restriction should be withdrawn, because both criteria for a restriction requirement are not met as set forth in MPEP § 803, namely that the inventions be independent or distinct and that there would be a serious and undue burden on the Examiner.

The applicants' request to withdraw the restriction was found unpersuasive because of the following reasons (summarized from the restriction paper):

The inventions of Groupings [I, II, and III], [IV and VI], and [V] are independent inventions because they are directed to different chemical and entity types regarding the critical limitations therein. For Groups I, II, and III; the critical feature is an androgen receptor modulator. For Groups IV and VI, the critical feature is a molecule or molecular complex of a three-dimensional crystal structure. For Group V, the critical feature is a machine-readable storage medium. The completely separate chemical and entity types of the invention Groups are often separately characterized and published in literature, thus adding to the search burden if all Groups were examined together. Also, processing that may connect two Groups does not prevent them from being considered distinct because enough processing can result in the production of any composition from another composition as long as the processing is not limited in occurrences such as subtractions, additions, and enzymatic action. Thus, the three Groupings

[I, II, and III], [IV and VI], and [V] are independent and/or distinct invention types for restriction purposes.

Inventions in Groups I, II, and III are related as product and the process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the androgen receptor modulator of Group II may be utilized in distinct usages as needed in Group I for a method for inhibiting growth of hormone-dependent tumor cells, in a method for identifying a selective androgen receptor modulator as in Group III, or alternatively, in x-ray crystallography studies. All of these usages are distinct as requiring distinct and different functions thereof without overlapping search due to different subject matter. This lack of overlapping searches documents the undue search burden if they were searched together.

The Examiner maintains the presence of independent and/or distinct inventions as well as a serious and undue search burden if all Groups were examined together.

The requirements are still deemed proper and are therefore made FINAL.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The present title is directed to androgen receptor modulators and methods for their identification, design, and use, whereas in contrast the elected claims include only a method for inhibiting growth of hormone-dependent tumor cells.

The information disclosure statement filed 10/15/01, 8/23/02, and 10/11/02 fail to comply with the provisions of 37 CFR 1.97, 1.98, and MPEP § 609, because for 10/15/01 IDS references AA-AB were never published and for 8/23/02 IDS references BM, BN, BP, CF-CI, CV-CX, FS-FU, and FW-FX were in a foreign language and JA-JB, KA-KB, KO-KP, and KR-KS do not have a listed date of publication. They have been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609, §III, ¶ C(1).

Claims herein under examination are 1-7 and 9.

Claim Rejections – 35 U.S.C. 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6)

the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of the skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

LACK OF SCOPE OF ENABLEMENT

Claims 1-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the atomic structural coordinate listing (Table A) of an androgen receptor-ligand binding domain (AR-LBD), does not reasonably provide enablement for a method of inhibiting the growth of hormone-dependent tumor cells by administering any selective androgen receptor modulator (SARM) that interacts with any androgen receptor complex. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicants state that one "drug design technique enabled in this invention is iterative drug design" (page 10, lines 34-35). Applicants further state that "[i]n iterative drug design, crystals of a series of protein/ligand complexes are obtained" followed by the determination of three-dimensional structures of each complex (page 11, lines 16-19). However, a method that relies on data from an unpredictable art such as protein crystallization would require clear and precise guidance for one skilled in the art to reliably use the said methods. As the science of protein crystallization is well known to be a trial and error procedure with unpredictable results (Drenth, page 1, lines 13-20), one skilled in the art would require clear and precise guidance to make any particular crystal in order to obtain structural coordinates for a three-dimensional

model. Accordingly, it would be very difficult for a skilled artisan to make crystal structures of other androgen receptor complexes beyond that mentioned in the instant case where specific coordinates are disclosed. Due to the unpredictability and difficulty of crystallizing proteins, it is unlikely that one of skill in the art would be able to make another crystal relying solely on the information for the crystal disclosed in the specification without undue experimentation. Again, due to the unpredictability in the art, a skilled artisan could not reasonably expect to make and use the structural coordinates from any androgen receptor complex based on generic guidelines of making crystals without undue experimentation.

Claims 9 is further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SARM compounds that were tested in vitro and in vivo to determine whether treatment was effective in remedying a condition in prostate tumors and various cells lines as seen in Examples 2-13 (pages 86-98), does not reasonably provide enablement for a method of treatment of all of the conditions listed in claim 9 by administering an selective androgen receptor modulator (SARM) in an effective amount. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim.

Without further data or sound scientific reasoning, it appears speculative whether these SARMs listed in the specification treat all of the conditions listed in claim 9. As pointed out by Garrard et al., finding effective drugs is not only difficult, but also unpredictable (col. 1, lines 57-67). With this in mind, additional evidence is necessary in order to satisfy the current lack of scope of enablement for the conditions listed in claim 9. Several options exist to overcome this lack of scope of enablement issue, such as supplying additional data supporting the effective

treatment conclusions listed in claim 9 or other scientific reasoning that would lead one of ordinary skill in the art to be able to make and/or use the present invention.

Claims Rejected Under 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claim 1 is vague and indefinite because, in line 4, the phrase "exhibits antagonist activity" does not include sufficient antecedent basis as to what the antagonist activity is directed. For example, in line 1, the method is directed to inhibiting growth, but said line 4 phrase lacks being antagonistic to growth. In claim 1, lines 2-3, a selective androgen receptor modulator is cited but without said line 4 phrase correspondingly stating that the antagonist activity is actually the modulation activity as in lines 2-3. As worded the "antagonist activity" in line 4 may include or even be exclusively directed to being antagonistic to some cellular constituent which is unrelated to an androgen receptor. Clarification of the claim via clearer claim wording including sufficient antecedent basis is requested. Claims 2-7 are also rejected due to their direct or indirect dependency from claim 1.

Claim 9 is rejected as vague and indefinite due to its reference to a non-elected claim. Correction is requested by only stating embodiments which are part of the elected claims.

Claim 9 is vague and indefinite due to the unclarity of citing an abbreviation, such as VEGF on line 8. Correction is suggested by amending in of the full name in parentheses.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. (e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thorpe et al. (P/N 6,004,554), in view of Zhi et al. (P/N 6,358,947) and Li et al. (P/N 6,469,024).

Thorpe et al. describe treating tumors by using immunological reagents to target tumor-associated vascular endothelial cells in combination with direct targeting of tumor cells (col. 3, lines 45-52 and Table II on col. 25-26). Thorpe et al. describe therapeutic agents that have cytotoxic or anticellular effect by suppressing growth or division of cells (col. 3, lines 57-64).

Thorpe et al. describe these methods and compositions as applicable to solid tumors, including carcinomas of the prostate (col. 4, lines 1-11 and Fig. 15A). Thorpe et al. describe a therapeutic method employing an antibody having high selectivity for tumor cells and little or no reactivity with the cell surface of normal endothelial cells (col. 5, lines 30-36). Thorpe et al. describe therapeutics showing no significant reactivity with normal tissues, including kidney, brain, liver, bone marrow, prostate, thyroid, muscle, skin, or other normal organ or tissue (col. 25-26, lines 64-67). Thorpe et al. describe and therefore suggest attaching other agents to target the toxin moiety to a tumor, such as hormones (col. 30, lines 34-43). Thorpe et al. do not specifically mention selective androgen receptor modulators.

Zhi et al. describe compounds that modulate a process mediated by androgen receptors (col. 19, lines 20-23), including male hormone response diseases (col. 19, lines 26-27). Zhi et al. describe a method of treating prostate adenocarcinomas, carcinomas, benign prostatic hypertrophy of prostate, and other hormone-dependent tumors by administering a pharmaceutically effective amount of a compound (col. 20, lines 9-25).

Li et al. describe methods for treating osteoporosis by administering a therapeutically effect amount of a compound which stimulates an increase in muscle mass (col. 5, lines 13-21 and col. 208, lines 50-52). Li et al. describe a method for increasing growth hormone levels by administering a compound (col. 5, lines 7-12). Li et al. describe using the compounds in combination with a selective androgen receptor modulator to treat, stimulate, and increase muscle mass, as well as reducing cachexia due to cancer (col. 44, lines 47-61). Li et al. describe using the compounds in combination with anti-tumor agents (col. 49, lines 1-4). Li et al. describe treating Alzheimer's disease (col. 45, line 51), anorexia (col. 45, lines 38-39), and

muscular atrophy due to physical inactivity and bed rest (col. 46, lines 24-26) by administering a therapeutically effective amount of a compound (col. 45, lines 3-8; col. 208, lines 32-35; and col. 209, lines 7-9).

Thorpe et al. state that significant advances in chemotherapy have been made for some tumors, while other types of tumors resist chemotherapeutic intervention (col. 1, lines 39-41). Thorpe et al. point out the key to developing successful antitumor agents is to design them to selectively kill tumor cells while exerting little effect against normal tissues (col. 1, lines 65-67 and col. 2, line 1). Thorpe et al. state this has been difficult because of the few qualitative differences between neoplastic and normal tissues (col. 2, lines 1-3). Thorpe et al. state much research has been has focused on identifying tumor-specific "marker antigens" (col. 2, lines 3-6). As Thorpe et al. state, modifications can be made without departing from the spirit and scope of their invention (col. 31, lines 48-53), a skilled artisan in the art would have reasonable expectation of success to enhance the methods for inhibiting and treating prostate tumors, as stated by Thorpe et al., by administering various compounds related to prostate, as stated by Zhi et al. and Li et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to include the administration of selective androgen receptor modulators (as stated by Zhi et al. and Li et al.) in the methods of inhibiting and treating prostate tumor cells (as stated by Thorpe et al.) with a reasonable expectation of success. The motivation to do so is given by Thorpe et al. who teach developing successful antitumor agents via selective target agents (col. 1, lines 65-67), and the teaching of Zhi et al. and Li et al. relating to compounds that target androgen receptors.

Thus, Thorpe et al., in view of Zhi et al. and Li et al. motivate the instant invention.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (703) 308-6043. The examiner can normally be reached Monday through Friday from 8 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

February 4, 2003

Ardin H. Marschel

ARDIN H. MARSCHEL
PRIMARY EXAMINER